Long-term follow-up of ophthalmic Graves' disease

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Sixteen patients with ophthalmic Graves' disease (clinically euthyroid with ophthalmopathy or exophthalmos) were followed up for 4.3 to 14.3 (mean 9.1) years to determine whether thyroid dysfunction developed and whether their ophthalmopathy progressed, regressed or remained stable. Five patients (31%) manifested hyperthyroidism or hypothyroidism, all before the end of the fifth year of follow-up. The ophthalmopathy was mild, and none of the patients required specific treatment. The thyroid function of patients with ophthalmic Graves' disease should be periodically monitored for at least 5 years.

On a suivi pendant 4,3 à 14,3 ans (en moyenne 9,1) 16 sujets présentant une maladie de Graves-Basedow ophtalmique, c'est à dire une ophtalmopathie ou une exophtalmie chez une personne cliniquement euthyroïdienne. On voulait savoir s'il surviendrait une dysthyroïdie et si l'ophtalmopathie serait en aggravation ou en régression ou si elle resterait stable. Tous les 16 sujets ont une ophtalmopathie de peu de gravité, ne nécessitant pas de traitement spécifique. Dans le délai de 5 ans d'observation, cinq d'entre eux (31%) sont soit hyperthyroïdiens, soit hypothyroïdiens. Il faut donc suivre de près la fonction thyroïdienne des porteurs d'une maladie de Graves-Basedow ophtalmique pendant au moins 5 ans.

Graves' disease is a systemic disorder characterized by one or more of the following clinical entities: hyperthyroidism due to diffuse thyroid hyperplasia, infiltrative ophthalmopathy and infiltrative dermopathy (pretibial myxedema).[1] Any of these clinical manifestations may occur independently of the others at any time in the course of the disease.

Rundle[2] recognized that the ophthalmopathy of Graves' disease may be present without hyperthyroidism or goitre, and Rundle and Wilson[3] used the term "ophthalmic form of Graves' disease" to describe the condition. The definition has since been broadened to include patients with thyroid enlargement that are euthyroid and have no history of hyperthyroidism.[4]

There is little information in the literature concerning the long-term prognosis of patients with ophthalmic Graves' disease. For the most part the follow-up in previous studies has been short[5-10] and the number of patients small.

We carried out a study to define the natural history of ophthalmic Graves' disease over a follow-up period of approximately 9 years to determine whether thyroid dysfunction developed and whether the ophthalmopathy progressed, regressed or remained stable.

Methods

Forty patients who were clinically euthyroid and had ophthalmopathy or exophthalmos were initially seen by one of us (I.R.H) at the Ottawa Civic Hospital between 1968 and 1975. Their charts were reviewed, and nine patients were excluded because of previous thyroid disorders (hyperthyroidism [in eight patients] and hypothyroidism [in one patient]). Two other patients were excluded because of elevated serum thyroxine (T_4) levels, and two patients with nonendocrine ophthalmopathy — one with a pontine glioma and the other with unilateral ptosis — were excluded. Of the remaining 27 patients 26 had normal serum T_4 levels initially; the other patient (no. 9) had an initial level, as determined by column chromatography, of 6.8 (normally 2.3 to 6.7) μg/dl (88 [normally 30 to 86] nmol/L) and a normal level 6 months later.

Of the 27 patients with ophthalmic Graves' disease 16 (59%) were seen in follow-up, 11 of

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them in 1984; the other 5 were followed up for a mean of 5.2 years before 1984. Eleven patients were lost to follow-up. Each patient gave a history and underwent a physical examination. With all the patients seen in 1984 we measured the serum levels of free T_4 (Gamma Coat [I-125] Free/Total T_4, Clinical Assays, Toronto), free triiodothyronine (T_3) (Free T_3 Amerlex RIA Kit, Amersham Corporation, Oakville, Ont.), total T_3 (determined by radioimmunoassay) (Tri Tab RIA, Nuclear Medical Laboratories, Toronto) and thyroid-stimulating hormone (TSH) (HTSH RIABEAD Diagnostic Kit, Abbott Laboratories, Toronto). Fourteen patients who were followed up were tested for antimicrosomal and antithyroglobulin antibodies (Sera-Tek Thyroglobulin Antibody Test, Reagent Kit, Sera-Tek Microsomal Antibody Test, Reagent Kit, Ames Division, Miles Laboratories Ltd., Toronto). Testing for T_3 suppression was performed in some of the patients.

The criterion for diagnosing hyperthyroidism was a serum free T_4 level greater than 28.5 pmol/L or a serum T_3 level greater than 2.92 nmol/L, as determined by radioimmunoassay. The criteria for diagnosing hypothyroidism were a serum TSH level greater than 7 mU/L and a serum free T_4 level lower than 11.5 pmol/L.

The ophthalmopathy was graded according to the classification accepted by the American Thyroid Association.[11] As well, an ophthalmopathy index based on this classification was computed for each patient.[12] A Hertel exophthalmometer was used to measure proptosis.

Statistical significance was determined with the chi-square method and the *t*-test for independent means.

Results

The group of patients that was lost to follow-up was similar to the group that was followed up (Table I).

The length of follow-up ranged from 4.3 to 14.3 (mean 9.1) years. During the follow-up period 5 of the 16 patients (31%) had a change in thyroid status: 1 became hypothyroid and later manifested hyperthyroidism, 2 became hypothyroid, and 2 became hyperthyroid (Fig. 1). All of these changes occurred before the end of the fifth year of follow-up.

Of the 16 patients 9 (56%), including the 5 with a change in thyroid status, had thyroid enlargement at some point during the follow-up period. Testing for T_3 suppression was performed in 12 of the 16 patients; nonsuppressibility was shown in 5 (42%), 3 of whom later manifested thyroid dysfunction. Nine of the 14 patients tested (64%) had antithyroid antibodies, and 4 of the 9 later manifested either hypothyroidism or hyperthyroidism.

Ten of the 16 patients (63%) had thyroid enlargement, T_3 nonsuppressibility or antithyroid antibodies. However, only five had clinical and biochemical evidence of thyroid dysfunction.

The degree of ophthalmopathy in the 16 patients ranged from class 1 to class 4. Two patients had unilateral involvement. The ophthalmopathy regressed in seven patients (44%); in one case there was total resolution over the follow-up period. Seven patients had stable eye disease, and in two there was mild progression during follow-up. Vision-threatening ophthalmopathy (class 5 or 6) requiring specific treatment did not develop in any of the patients. One patient underwent unilateral orbital decompression for cosmetic reasons. Two patients were receiving corticosteroid therapy for other disorders, and the ophthalmopathy regressed in both. The mean ophthalmopathy index did not change significantly during the follow-up period.

Discussion

Estimates of the incidence of ophthalmopathy in Graves' disease range from 40% to 90%.[13] Ophthalmopathy was shown to be present in a large proportion of patients without clinically evident eye disease by demonstration of an increase in intraocular pressure on upward gaze.[14] Orbital ultrasonography showed changes characteristic of infiltrative ophthalmopathy in 63% to 93% of such patients,[15] whereas computed tomography of the orbit revealed extraocular muscle enlargement in 40% of patients without clinically apparent ophthalmopathy.[16] The ophthalmopathy characteristic of Graves' disease has been reported to occur in

Table I — Initial characteristics of patients with ophthalmic Graves' disease who were or were not followed up

Characteristic	Group lost to follow-up (n = 11)	Group followed up (n = 16)
Age, yr*		
Mean	41.7	43.8
Range	15–72	29–67
Female:male ratio*	4.5:1	3.0:1
Degree of ophthalmopathy, no. (and %) of patients*†		
Classes 1–2	8 (73)	8 (50)
Classes 3–6	3 (27)	8 (50)
Mean ophthalmopathy index*	1.36	2.13
Thyroid function, no. (and %) of patients		
Goitre	2 (18)	4 (25)
Antithyroid antibodies	1 (25) (n = 4)	5 (56) (n = 9)
Triiodothyronine nonsuppressibility	4 (67) (n = 6)	5 (42) (n = 12)
Family history of thyroid dysfunction	3 (27)	5 (31)

*Differences were not statistically significant.
†Graded according to the American Thyroid Association classification.[11]

patients with Hashimoto's thyroiditis[17] and in hypothyroidism.[18]

Previous follow-up studies of patients with ophthalmic Graves' disease have given different results (Table II).[5-10] In the study by Franco and colleagues[6] the two patients in whom hypothyroidism developed both had Hashimoto's thyroiditis. Nine patients in the study by Foldes[7] initially had elevated serum T_3 levels and "subclinical T_3 thyrotoxicosis"; two of them later became overtly hyperthyroid. The largest series were those of Teng and Yeo[8] and Tamai and associates.[10] Teng and Yeo found that 30% of their 27 patients had a change in thyroid status, 7 becoming hypothyroid and 1 becoming hyperthyroid. Tamai and associates reported that thyroid dysfunction developed in 48% of their 27 patients, 9 becoming hyperthyroid and 4 becoming hypothyroid. The changes in ophthalmopathy were assessed in only three of these studies.[6-8].

In our study 31% of the 16 patients followed up had a change in thyroid status. This figure is similar to that reported by Teng and Yeo but is much lower than that reported by Tamai and associates. Also, most of the patients with a change in thyroid status in Teng and Yeo's study became hypothyroid (7 of 8), whereas 9 of 13 patients in the study by Tamai and associates became hyperthyroid. In our study equal numbers of patients became hyperthyroid or hypothyroid (one had hyperthyroidism preceded by hypothyroidism). The reason for these differences is not clear. However, the proportions of patients with goitre (73%) or T_3 nonsuppressibility (71%) in the study by Tamai and associates were higher than those in Teng and Yeo's study or our study. As well, 63% of the patients in the study by Tamai and associates had an impaired response or no response to thyrotropin-releasing hormone, compared with 30% in Teng and Yeo's study. These differences in thyroid function may explain the different clinical behaviour of the various groups of patients.

In our study, which had the longest follow-up period, all changes in thyroid status occurred before the end of the fifth year of follow-up.

Hypothyroidism preceding hyperthyroidism, as in our patient 2, is rare but has previously been reported.[19]

The ophthalmopathy in our patients was mild and never required specific treatment. The changes

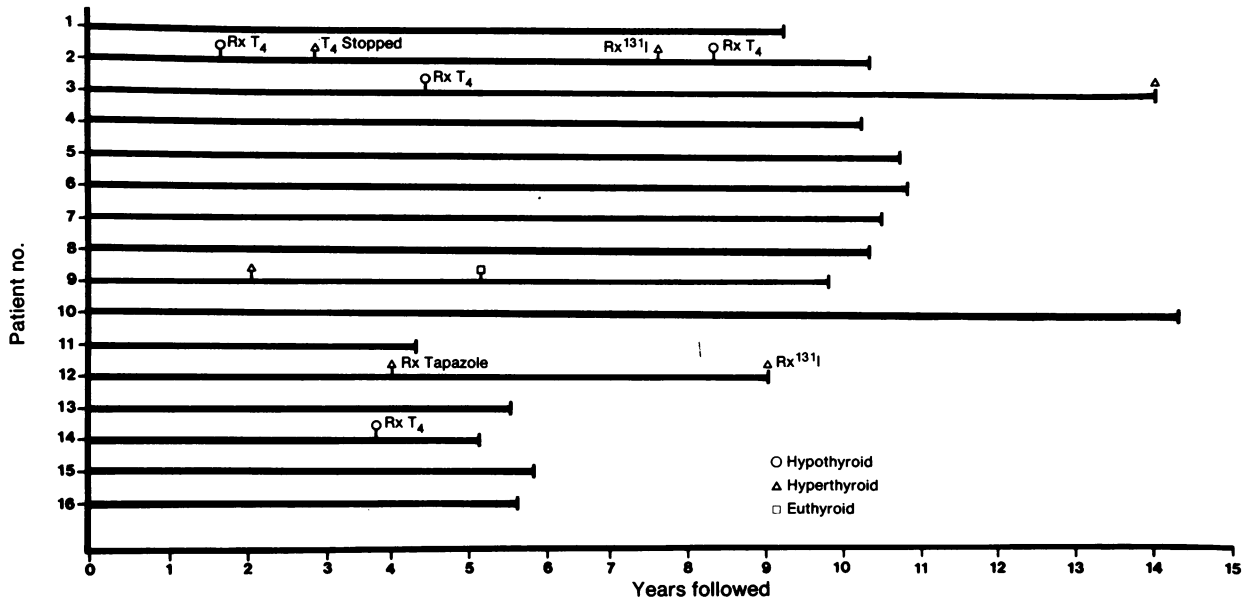

Fig. 1 — Change in thyroid status over follow-up period.

Table II — Results of follow-up studies in patients with ophthalmic Graves' disease

Investigator	No. of patients	Length of follow-up	Thyroid status, no. of patients*			Ophthalmopathy, % of patients		
			Euthyroid	Hyperthyroid	Hypothyroid	Remained stable	Regressed	Progressed
Burke[5]	8	Mean 6 yr	8	0	0	–	–	–
Franco et al[6]	11	Mean 4 yr	8	1	2	0	82	18
Foldes[7]	13	Up to 24 mo	9	3	1	24	38	38
Teng et al[8]	27	3 yr	19	1	7	20	67	13
Cennamo et al[9]	15	1 yr	14	0	1	–	–	–
Tamai et al[10]	27	Up to 3 yr	14	9	4	–	–	–
Present study	16	Mean 9.1 yr	11	3	3	44	44	12

*In the present study one patient became hypothyroid then, later, hyperthyroid.

over time tended toward improvement. Our figures are similar to those reported by Teng and Yeo; however, more of their patients had progression, and a number required systemic therapy with corticosteroids, orbital radiotherapy or surgery.

In conclusion, patients with ophthalmic Graves' disease demonstrate various abnormalities in thyroid function. Over a long period of follow-up a large proportion manifest clinically evident thyroid disease. The ophthalmopathy is usually mild. The thyroid function of these patients should be periodically monitored for at least 5 years.

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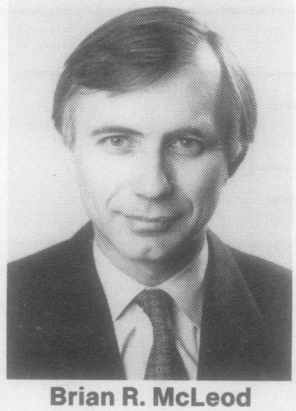
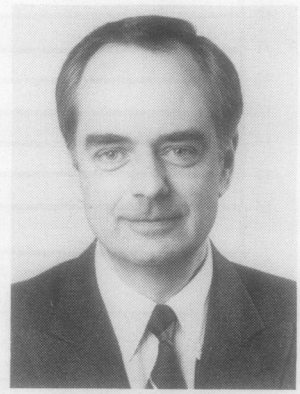


Brian R. McLeod



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Dr. John L. Zabriskie, Chairman and President of Merck Frosst Canada Inc. announces the following senior executive appointments:

Mr. Hubert J. Martel becomes Senior Vice-President of the Company in which capacity he will be responsible for planning, organizing and directing all aspects of Merck Frosst's public, professional and government relations programs. Formerly Vice-President Marketing, Mr. Martel brings over 30 years of pharmaceutical industry experience to his new assignment.

Mr. Brian R. McLeod becomes Vice-President Marketing. Mr. McLeod joined the Company in 1969 and since then has held several progressively more senior sales and marketing management positions. Since 1982 he has headed up the Company's field sales organization.

Mr. Gerald J. Gallivan assumes responsibility for the overall direction of the Company's pharmaceutical sales force as Executive Director - Sales. Mr. Gallivan has over 20 years of diversified management experience with Merck Frosst.

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